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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,201	06/27/2005	Michael Mandola	UMD-0097	2039

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/532,201	MANDOLA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence received 5/13/08. All previously pending claims were cancelled and claim 21 was added. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive to place the claims in condition for allowance for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Election/Restrictions

2. Applicant states that the election was made without traverse and requests that the record be corrected to note as much. However, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 21 is indefinite because the claim requires detecting "the presence of a +6 bp/1494 3' untranslated region polymorphism." It is not clear how one detects a polymorphism in an individual. A polymorphism is difference in a particular nucleic acid sequence among

individuals. Therefore, in a single individual, one could detect the nucleotides present in a particular portion of nucleic acid molecule, but one could not detect differences among individuals in a single person.

Priority

6. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/420,164, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The provisional application does not discuss the +6/-6 deletion polymorphism which is referred to in claim 21. Furthermore, the provisional application does not provide enabling support for the claimed invention for at least the same reasons that the instant specification does not provide enabling support for the claimed invention. Therefore, the filing date of the instant claim is the effective filing date of this application: 10/21/03.

Applicant states on page 4 of the response that this analysis is disagreed with, but provides no reasoning or argument to support this position. In particular, applicant does not address where the provisional application discusses the +6/-6 deletion polymorphism which is mentioned in the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection under Ulrich et al. is withdrawn and not applied to the newly added claim. Ulrich et al. do detect the alleles present in the so called 28-bp repeat polymorphism and the 3'UTR 6-bp deletion polymorphism, and further teach that the 3R/3R genotype is associated with an increased risk of developing cancer in patients low or medium folate intake (Figure 1 and p.3363 2nd column). Ulrich et al. further teach that the 6-bp deletion is not associated with risk of colorectal adenoma, and therefore, the association with the 3R/3R genotype would be present with the + or - 6bp alleles. However, they do not provide adequate evidence to support the assertion that the presence of 3R/3R and +6bp alleles indicates that an individual HAS colon cancer, only that certain associations exist. In fact, Table 1 shows that all alleles were identified in both cases and controls.

8. The rejections under 102(a) and/or (b) as being anticipated by Mandola et al., Kawakimi et al. and Lenz et al. are WITHDRAWN in view of the amendment of the claim to positively require detecting nucleotides present in both the 5' and 3' regions of the thymidylate synthase nucleic acid molecules.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claim is drawn to a method for determining whether an individual has colorectal cancer. The active process steps recited in the claim detecting the presence of a 3R/3R, 3R/3RV, 2R/2R, 2R/3R, or 2R/3RV construct in the 5' region of the TS nucleic acid molecule and detecting the presence of a +6 bp/1494 3' untranslated region polymorphism in the TS nucleic acid molecule. The claim sets that the presence of the 3R/3R construct and +6 bp/1494 3' untranslated region polymorphism indicates that the subject has colorectal cancer. Thus, the nature of the invention requires the knowledge of a reliable association between the presence of particular alleles of the TS gene and the presence of colorectal cancer.

Quite simply, the plain language of the claim states that when a particular genotype is present it can be concluded that colorectal cancer is present.

The specification provides experiments beginning at ¶0058, but the specification does not provide a single experiment wherein alleles of the polymorphisms analyzed relative to populations of individuals with colorectal cancer versus healthy control individuals. Furthermore, the specification does not provide any definitive evidence to support the assertion

that when the 3R/3R construct and +6 bp/1494 3' untranslated region polymorphism are present colorectal cancer is also present.

In ¶0061 the specification states that there is a G→C SNP in the 2nd repeat of the 3R allele of the TS promoter polymorphism, that the C allele alters the USF consensus binding ability and that the more non-variant 3R alleles present the worse the response to 5-FU based chemotherapy drugs.

Applicants confirmed that there are two single base changes in the last 28 bp repeat of both the 2R and 3R genotypes, and applicant further identified a single nucleotide polymorphism within the second repeat of the 3R allele (see ¶ 0072 and Figure 1). Applicants refer to the newly identified allele of the SNP as the 3RV allele and as the "variant sequence."

Applicants teach that there is a USF E-box consensus element in the first repeat of the 2R genotype and in the first and second repeats of the 3R genotype. The SNP that applicants identified in the second repeat of the 3R genotype alters this element (¶ 0074). The specification teaches that neither unphosphorylated nor phosphorylated forms of USF-1 showed affinity to the variant sequence in vitro (¶ 0081). Applicants used a chromatin immunoprecipitation assay to show that USF-1 and USF-2 bind the TS locus which includes the tandem repeats and the E-box elements (¶0084).

The specification teaches that a 3RV construct displays similar transcriptional activity as a 2R construct which is lower than the activity of the 3R construct (Figure 5B, ¶ 0088).

The specification teaches that the G→C SNP was only observed in the second repeat of 3R genotypes and that the frequency of the C allele among the second repeat of the 3R was 56% among all 3R carriers in a group of non-Hispanic whites (¶0093).

The specification teaches the analysis of response of 40 patients having colorectal cancer to treatment with 5-fluorourocil (5-FU). No significant response was observed when the genotypes 3R/3R, 2R/3R and 2R/2R were considered. However, reclassifying the patients based on predicted high and low TS expression using the repeat polymorphism and the SNP polymorphism resulted in a significant result with patients having low-expression TS genotypes having an improved response rate relative to patients with high-expression TS genotypes (¶ 0095-¶0098).

Applicants further completed experiments to characterize the effects of the so called -6 bp/1494 deletion polymorphism, and demonstrate that there are no major mRNA instability or translational silencing elements within the TS-3'UTR (¶0103-0109). Applicant further demonstrated that the -6 bp/1494 construct has decreased mRNA stability compared with +6bp constructs, and that the -6 bp allele has an increased rate of mRNA degradation (¶0110-0114). Applicants found that patients homozygous for the +6bp allele had significantly higher TS mRNA expression in colorectal tumor tissue than individuals homozygous for the -6bp allele (¶0117).

The specification teaches that in relation to cardiovascular disease treatment, clinicians can determine if a subject is at a higher risk for CVD by looking at the number of non-variant alleles, teaching that the levels of folate will likely be lower and homocysteine will likely be higher than in subjects with more 2R and/or 3RV alleles, thus making that individual more susceptible to CVD (¶ 0067).

The conclusions set forth in the instant claims are not based on empirical association studies between genotypes and risk or incidence of any type of cancer or cardiovascular disease.

Instead, they are based upon assumptions in view of the potential effect of the polymorphisms on total folate load in patients and the potential effects of those folate loads on disease risk. However, it is highly unpredictable when or if these assumptions may actually be true or reproducible.

Zhang et al. found that total folate intake is not associated with overall risk of breast cancer, but may be a mitigate risk of breast cancer associated with alcohol consumption. This is relevant since the conclusions set forth in the instant claim are based, in part, about assumptions concerning the effects of folate metabolism on predisposition to or the presence of disease. However, the assumptions about folate metabolism were not robustly established at the time of filing, especially not with regard to all possible types of cancer, including colorectal cancer.

Applicants' claim recites that an individual with the 3R/3R construct in the 5' region of the TS gene and a single +6 bp allele in the 3' untranslated region polymorphism has the highest probability of developing cancer. However, the prior art at the time of filing demonstrates that whether or not this is universally true is highly unpredictable. Ulrich et al. found that for patients with the 3R/3R alleles and high folate intake there is a decreased risk of colorectal adenoma (p. 3363, Urlich et al. 2002, as cited in IDS). This is opposite of the assertions set forth in the instant claim which state that the 3R/3R construct confers a heightened predisposition to cancer or cardiovascular disease. Among individuals with the 2R/2R genotype and high folate intake there was an increased risk for colorectal adenoma (p. 3362). Further, Urlich et al. teach that "[t]he finding of a decreased risk associated with lower TS expression in the presence of low-folate intake (Fig. 1) was unexpected (p. 3363)." It is apparent that the allele status of an individual is not sufficient to predict colorectal carcinogenesis.

Ulrich et al. found that the allele status of the 6bp allele is not predictive of the risk of colorectal adenomas (p. 3363). Urlich et al. state that "[a]lthough one might expect results similar to those for the TSER polymorphism, because of linkage between the two polymorphisms, these findings illustrate that 'imperfect' disequilibrium may result in different associations with disease phenotypes (p. 3363)." Lenz et al. (cited in IDS) found results that appear to be **opposite** of those suggested in the claim- namely that it is the presence of the deletion allele (the -6 allele) which confers increased risk of the presence of colorectal cancer.

There is no example or evidence in the prior art or in the instant specification which suggests that the presence of any particular allele of the TS gene is sufficient to conclude that an individual has colorectal cancer, as currently claimed. In fact, such a statement, which is encompassed by the recitation in the claims, is contraindicated by the fact that all alleles can be routinely identified in healthy individuals. Even if the polymorphism is associated with developing colorectal cancer, it does not necessarily follow that the simple presence of particular alleles means colorectal cancer is present, as currently claimed.

The practice of the claimed invention would require extensive experimentation to discover whether or not the relationship set forth in claim 21 is true- and the state of the art suggests that in fact the relationship could not be confirmed- that is, the presence of the alleles as recited does not provide a method for determining whether an individual HAS colorectal cancer. For the polymorphisms specifically recited in the claim, there is no evidence of record which suggests that the relationships set forth in the "wherein" clause are actually reliable in view of effects observed in actual populations. Extensive experimentation, which is unlikely to succeed would have to be undertaken to establish between the recited alleles and colorectal cancer, since

there is no established universal relationship between the presence of colorectal cancer and TS alleles.

Thus, having carefully considered all of these factors, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks

Applicant traverses the rejection for lack of enablement beginning on page 8 of the response. Applicant states on page 8 that the claim as currently presented is enabled by the specification specifically Table 1 which provides the distribution of the 5'-TS repeat polymorphism alleles among 99 non-hispanic white individuals with colorectal cancer, and that this data shows the 3R allele is more frequently present in individuals with colorectal cancer. The data indeed shows that in this population the 3R allele is most frequent, however, there is no comparison to a population of healthy controls. There is no showing that the presence of this allele in combination with the +6bp allele is sufficient to conclude that colorectal cancer is present. The same deficiencies are present with regard to the data provided for the +6bp allele. Many issues regarding the lack of showing in the specification and the highly unpredictable nature of this particular technology area are discussed in the rejection and are not satisfied by applicant's amendments or remarks. The rejection is modified and applied to the newly added claim.

Conclusion

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

July 31, 2008